Search Strategy

FILE 'USPATFULL' ENTERED AT 12:21:24 ON 12 DEC 2002

		E	LITWIN V M/IN
L1	7	S	E4
		E	ALLAWAY G P/IN
L2	14	S	E4
L3	8	S	L2 NOT L1
		E	MADDON P J/IN
L4	25	S	E4
L5	13	S	L4 NOT (L1 OR L2)
L6	36108	S	MONOCLONAL ANTIBOD?
L7	8500	S	L6 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L8	5606	S	L7 AND FUSION
L9	5510	S	L8 AND (INHIBIT? OR BLOCK? OR NEUTRALIZ?)
L10	757	S	L9 AND (CHEMOKINE OR CORECEPTOR OR ACCESSORY MOLECULE?)
L11	419	S	L10 AND ANTIBOD?/CLM
L12	31	S	L11 AND (CD11A OR CD18)
L13	917	S	(CD11A OR CD18)
L14	719	S	L13 AND L6
L15	370	S	L14 AND ANTIBOD?/CLM
L16	57	S	L15 AND (CD11A/CLM OR CD18/CLM)
L17	54	S	L16 NOT L12

FILE 'WPIDS' ENTERED AT 12:50:49 ON 12 DEC 2002

		E	LITWIN V M/IN
L18	9	S	E3
		E	ALLAWAY G P/IN
L19	16	S	E3
		E	MADDON P J/IN
L20	28	S	E3
L21	10044	S	MONOCLONAL ANTIBOD?
L22	656	S	L21 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L23	83	S	L22 AND FUSION
L24	53	S	L23 AND (INHIBIT? OR BLOCK? OR NEUTRALIZ?)
L25	8	S	L24 AND (CHEMOKINE OR CO-RECEPTOR OR ACCESSORY MOLECULE)
L26	55	S	L21 AND (CD11A OR CD18 OR LFA-1)

FILE 'MEDLINE' ENTERED AT 12:52:47 ON 12 DEC 2002

		E	LITWIN V M/AU
L27	10	S	E1
		E	ALLAWAY G P/AU
L28	21	S	E3
L29	19	S	L28 NOT L27
		E	MADDON P J/AU
L30	37	S	E3-E4
L31	27	S	L30 NOT (L27 OR L28)
L32	113663	S	MONOCLONAL ANTIBOD?
L33	2349	S	L32 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L34	302	S	L33 AND (FUSION OR CELL-CELL TRANSMISSION)
L35	217	S	L34 AND (INHIBIT? OR BLOCK? OR NEUTRALIZ?)
L36	7	S	L35 AND (CD11A OR CD18 OR LFA-1)

L1 ANSWER 3 OF 7 USPATFULL
2002:24365 Method for preventing HIV-1 infection of CD4+ cells.
Allaway, Graham P., Mohegan Lake, NY, United States
Litwin, Virginia M., Fayetteville, NY, United States
Maddon, Paul J., Elmsford, NY, United States
Olson, William C., Ossining, NY, United States
Progenics Pharmaceuticals, Inc., Tarrytown, NY, United States (U.S. corporation)
US 6344545 B1 20020205
APPLICATION: US 1997-831823 19970402 (8)
PRIORITY: US 1996-19715P 19960614 (60)
US 1996-14532P 19960402 (60)
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention provides methods for inhibiting fusion of HIV-1 to CD4.sup.+ cells which comprise contacting CD.sup.4+ cells with a non-chemokine agent capable of binding to a chemokine receptor in an amount and under conditions such that fusion of HIV-1 to the CD4.sup.+ cells is inhibited. This invention also provides methods for inhibiting HIV-1 infection of CD4.sup.+ cells which comprise contacting CD4.sup.+ cells with a non-chemokine agent capable of binding to a chemokine receptor in an amount and under conditions such that fusion of HIV-1 to the CD4.sup.+ cells is inhibited, thereby inhibiting the HIV-1 infection. This invention provides non-chemokine agents capable of binding to the chemokine receptor and inhibiting fusion of HIV-1 to CD4.sup.+ cells. This invention also provides pharmaceutical compositions comprising an amount of the non-chemokine agent capable of binding to the chemokine receptor and inhibiting fusion of HIV-1 to CD4.sup.+ cells effective to prevent fusion of HIV-1 to CD4.sup.+ cells and a pharmaceutically acceptable carrier.
CLM What is claimed is:
1. A method of inhibiting HIV-1 infection of a CD4+ cell which comprises contacting the CD4+ cell with an antibody or portion of an antibody capable of binding to a chemokine receptor on the surface of the CD4+ cell in an amount and under conditions such that fusion of HIV-1 or an HIV-1 infected cell to the CD4+ cell is inhibited, thereby inhibiting HIV-1 infection of the CD4+ cell.

2. The method of claim 1, wherein the chemokine receptor is a CCR5 chemokine receptor.

3. The method of claim 1, wherein the CD4+ cell is a PM-1 cell.

4. The method of claim 1, wherein the CD4+ cell is a primary CD4+ T-cell.

5. The method of claim 1, wherein the CD4+ cell is a PMBC cell.

6. The method of claim 1, wherein the antibody is a monoclonal antibody.

L1 ANSWER 4 OF 7 USPATFULL
2001:218025 Compounds capable of inhibiting HIV-1 infection.
Litwin, Virginia M., Fayetteville, NY, United States
Allaway, Graham P., Cheshire, Great Britain
Maddon, Paul J., New York, NY, United States
Progenics Pharmaceuticals, Inc. (U.S. corporation)
US 2001046512 A1 20011129
APPLICATION: US 2001-891062 A1 20010625 (9)
DOCUMENT TYPE: Utility; APPLICATION.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention provides an antibody capable of specifically inhibiting the fusion of an HIV-1 envelope glycoprotein cell with an appropriate CD4.sup.+ cell without cross reacting with the HIV-1 envelope glycoprotein or CD4 and capable of inhibiting infection by one or more strains so HIV-1. This antibody is then used to identify a molecule which is important for HIV infection. Different uses of the antibody and the molecule are described.

CLM What is claimed is:

1. An antibody capable of specifically inhibiting the fusion of an HIV-1 envelope glycoprotein cell with an appropriate CD4.sup.+ cell without cross reacting with the HIV-1 envelope glycoprotein or CD4 and capable of inhibiting infection by one or more strains of HIV-1.

2. A monoclonal antibody of claim i.

3. A hybridoma cell line producing the monoclonal antibody of claim 2.

4. A chimeric monoclonal antibody of claim 2.

5. A humanized monoclonal antibody of claim 4.

6. A human monoclonal antibody of claim 2.

7. A single chain antibody or an antigen binding antibody fragment of claim 2.

8. A monoclonal antibody capable of competitively inhibiting the binding of the monoclonal antibody of claim 2 to its target molecule.

9. The monoclonal antibody of claim 2, 4, 3, 6, 7, or 8 labelled with a detectable marker.

10. A monoclonal antibody of claim 9 wherein the detectable marker is a radioactive isotope, enzyme, dye or biotin.

11. A pharmaceutical composition comprising the complete or a portion of the monoclonal antibody of claim 2, 4, 5, 6, 7 or 8 and a pharmaceutically acceptable carrier.

12. A method of inhibiting HIV-1 infection in a subject comprising administering an effective amount of the pharmaceutical composition of claim 11 to the subject.

13. An isolated nucleic acid molecule encoding the complete or a portion of the light chain protein of the monoclonal antibody of claim 2, 4, 5, 6 or 8.

14. An isolated nucleic acid molecule encoding the complete of a portion of the heavy chain protein of the monoclonal antibody of claim 2, 4, 5, 6 or 8.

15. An isolated nucleic acid molecule encoding the single chain antibody of claim 7.

16. A vector comprising the nucleic acid molecule of claim 13, 14 or 15 operably linked to a promoter of RNA transcription.

17. A vector comprising the nucleic acid molecules of claims 13 and 14 each operably linked to a promoter of RNA transcription.

18. A host vector system comprising one or more vectors of claim 16 or 17 in a suitable host cell.

19. A host vector system of claim 18, wherein the suitable host cell is selected from a group consisting of a bacterial cell, an insect cell, a yeast cell or a mammalian cell.

20. The molecule specifically recognized by nhe monoclonal antibody of claim 1.

21. A glycoloipd molecule of claim 20.

22. A polypeptide molecule of claim 20.

23. An isolated nucleic acid molecule encoding the complete or a portion of the polypeptide of claim 22.

24. A multichain polypeptide molecule comprising the polypeptide of claim 22.

25. A soluble protein comprising a portion of the polypep-ide of claim 22 or 24.

26. A pharmaceutical composition comprising an effective amount of the soluble protein of claim 25 to inhibit HIV-1 infection and a pharmaceutically acceptable carrier.

27. A method of inhibiting HIV-1 infection in a subject comprising administering an effective amount of the pharmaceutical composition of claim 26 to the subject.

28. An isolated nucleic acid molecule encoding the complete or a portion of a polypeptide of the multichain polypeptide molecule of claim 24.

29. A vector comprising the nucleic acid molecule of claim 23 or 28 operably linked to a promoter of RNA transcription.

30. A host vector system comprising the vector of claim 29 in a suitable host cell.

31. A host vector system of claim 30, wherein the suitable host cell is a selected from a group consisting of a bacterial cell, an insect cell, a yeast cell or a mammalian cell.

32. A method for identifying inhibitors of HIV-1 infection comprising steps of: (a) contacting an effective amount of a compound with a system which contains HIV-1 gp120, HIV-1 gp41 or a fragment thereof with the molecule of claim 20 under conditions permitting formation of a complex between HIV-1 gp120, HIV-1 gp41 or a fragment thereof and the molecule, so as to inhibit such formation; and (b) determining the amount of complex formed; and (c) comparing the amount determined in step (b) with the control which is without the addition of the compound, a decrease in the complex formation indicating that the compound is capable of inhibiting HIV-1 infection.

33. A method of claim 32, wherein the compound is not previously known.

34. The compound identified by claim 33.

35. A pharmaceutical composition comprising the compound identified by the method of claim 32 and a pharmaceutically acceptable carrier.

36. A method of inhibiting HIV-1 infection in a subject comprising administering an effective amount of the pharmaceutical composition of claim 35 to the subject.

37. A kit for identifying inhibitors of HIV-1 infection which comprises, in separate compartments: (a) purified HIV-1 gp120, HIV-1 gp41 or a fragment thereof; and (b) the molecule of claim 20.

38. A transgenio nonhuman animal which comprises an isolated DNA molecule encoding the molecule of claim 22 or 24.

39. The transgenic nonhuman animal of claim 38 further comprising an isolated DNA molecule encoding the full-length or portion of the CD4 molecule sufficient for binding the HIV-1 envelope glycoprotein.

L3 ANSWER 1 OF 8 USPATFULL
2002:178733 Assay for detection of viral fusion inhibitors.
Wild, Carl T., Gaithersburg, MD, UNITED STATES
Allaway, Graham P., Darnestown, MD, UNITED STATES
US 2002094521 A1 20020718
APPLICATION: US 2001-779451 A1 20010209 (9)
PRIORITY: US 2000-235901P 20000928 (60)
US 2000-181543P 20000210 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention is directed to a methods for identifying compounds that inhibit or prevent infection of cells by enveloped viruses such as HIV-1 by preventing or disrupting conformational changes in the viral transmembrane protein that are required for virus fusion with those cells, and the compounds discovered by such methods. The invention also includes using these assays as diagnostic assays to detect antibodies in virus infected individuals that inhibit the viral entry processes.

L3 ANSWER 4 OF 8 USPATFULL
2002:17437 Method for generating immunogens that elicit neutralizing antibodies against fusion-active regions of HIV envelope proteins.
Wild, Carl T., Gaithersburg, MD, UNITED STATES
Allaway, Graham P., Darnestown, MD, UNITED STATES
US 2002010317 A1 20020124
APPLICATION: US 2001-809060 A1 20010316 (9)
PRIORITY: US 2000-189981P 20000317 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The current invention relates to methods of generating immunogens that elicit broadly neutralizing antibodies which target regions of viral envelope proteins such as the gp 120/gp41 complex of HIV-1. More specifically, the current invention involves using stabilizing peptides modeling the .alpha.-helical regions of the ectodomain of the HIV-1 transmembrane protein to stabilize fusion-active intermediate structures which can be used as vaccine immunogens.

L3 ANSWER 8 OF 8 USPATFULL
1998:122515 Synergistic composition of CD4-based protein and anti-HIV-1 antibody, and methods of using same.
Allaway, Graham P., Mohegan Lake, NY, United States
Maddon, Paul J., New York, NY, United States
Progenics Pharmaceuticals, Inc., Tarrytown, NY, United States (U.S. corporation)
US 5817767 19981006
APPLICATION: US 1993-21879 19930224 (8)

DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention is directed to compositions containing CD4-based immunoconjugates and antibodies specific for the envelope glycoprotein of human immunodeficiency virus type 1 (HIV-1). The CD4-based immunoconjugates comprise a portion obtained from CD4 conjugated to a heavy or light chain region obtained from IgG2. The CD4-immunoconjugates can be CD4-IgG2 chimeric heavy chain homodimers whose chains are encoded by the expression vector designated CD4-IgG2-pcDNA1 having ATCC Accession No. 40952, or heterotetramers having chimeric heavy chains encoded by the expression vector designated CD4-IgG2HC-pRcCMV having ATCC Accession No. 75193 and chimeric light chains encoded by the expression vector designated CD4-kLC-pRcCMV having ATCC Accession No. 75194. The compositions of the invention act synergistically to neutralize HIV-1.

L17 ANSWER 31 OF 54 USPATFULL
2000:31527 Humanized anti-CD11a antibodies.
Jardieu, Paula M., San Francisco, CA, United States
Presta, Leonard G., San Francisco, CA, United States
Genentech, Inc., South San Francisco, CA, United States (U.S. corporation)
US 6037454 20000314
APPLICATION: US 1997-974899 19971120 (8)
PRIORITY: US 1996-31971P 19961127 (60)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Humanized anti-CD11a antibodies and various uses therefor are disclosed. The humanized anti-CD11a antibody may bind specifically to human CD11a I-domain, have an IC50(nM) value of no more than about 1 nM for preventing adhesion of Jurkat cells to normal human epidermal keratinocytes expressing ICAM-1, and/or an IC50 (nM) value of no more than about 1 nM in the mixed lymphocyte response assay.
CLM What is claimed is:
1. A humanized anti-CD11a antibody which binds specifically to human CD11a I-domain, said antibody containing a heavy chain variable region comprising the amino acid sequence of (a) CDR2 (SEQ ID NO:11), (b) CDR1 (SEQ ID NO:10), CDR2 (SEQ ID NO:11) and CDR3 (SEQ ID NO:12) or (c) SEQ ID NO:5.

2. The humanized anti-CD11a antibody of claim 1 having a heavy chain variable region comprising the amino acid sequence of CDR1 (SEQ ID NO:10), CDR2 (SEQ ID NO:11) and CDR3 (SEQ ID NO:12) of humanized antibody MHM24 (F(ab)-8.

3. The humanized anti-CD11a antibody of claim 2 comprising the amino acid sequence of SEQ ID NO:5.

4. The humanized anti-CD11a antibody of claim 1 having a light chain variable region comprising the amino acid sequence of CDR1 (SEQ ID NO:13), CDR2 (SEQ ID NO:14) and CDR3 (SEQ ID NO:15) of humanized MHM24 F(ab)-8.

5. The humanized anti-CD11a antibody of claim 4 comprising the amino acid sequence of SEQ ID NO:2.

6. The humanized anti-CD11a antibody of claim 1 having a light chain variable region comprising the amino acid sequence of SEQ ID NO:5 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:2.

7. The humanized anti-CD11a antibody of claim 1 which is a full length antibody.

8. The humanized anti-CD11a antibody of claim 7 which is a human IgG.

9. The humanized anti-CD11a antibody of claim 1 which is an antibody fragment.

10. The humanized anti-CD11a antibody of claim 9 wherein the antibody fragment is a F(ab').sub.2.

11. A labeled antibody comprising the humanized anti-CD11a antibody of claim 1 bound to a detectable label.

12. An immobilized antibody comprising the humanized anti-CD11a antibody of claim 1 bound to a solid phase.

13. A conjugate comprising the humanized anti-CD11a antibody of claim 1 bound to a cytotoxic agent.

14. A method for determining the presence of CD11a protein comprising exposing a sample suspected of containing the CD11a protein to the humanized anti-CD11a antibody of claim 1 and determining binding of said antibody to the sample.

15. A kit comprising the humanized anti-CD11a antibody of claim 1 and instructions for using the humanized anti-CD11a antibody to detect the CD11a protein.

16. Isolated nucleic acid encoding the humanized anti-CD11a antibody of claim 1.

17. A vector comprising the nucleic acid of claim 16.

18. A host cell comprising the vector of claim 17.

19. A process of producing a humanized anti-CD11a antibody comprising culturing the host cell of claim 18 so that the nucleic acid is expressed.

20. The process of claim 19 further comprising recovering the humanized anti-CD11a antibody from the host cell culture.

21. The process of claim 20 wherein the humanized anti-CD11a antibody is recovered from the host cell culture medium.

22. The humanized anti-CD11a antibody of claim 1, having at least one of the following properties: (a) binds human CD11a with a K.sub.d value of no more than about 1.times.10.sup.-8 M, (b) has an IC50 (nM) value of no more than about 1 nM for preventing adhesion of Jurkat cells to normal human epidermal keratinocytes expressing ICAM-1, or (c) has an IC50 (nM) value of no more than about 1 nM in a mixed lymphocyte response assay.

23. The humanized anti-CD11a antibody of claim 1, having human kappa I consensus light chain framework residue 66L.

24. The humanized anti-CD11a antibody of claim 1, having all human kappa I consensus light chain framework residues.

25. The humanized anti-CD11a antibody of claim 1, having human V.sub.H subgroup III consensus heavy chain framework residue 93H.

26. A humanized anti-CD11a antibody which binds specifically to human CD11a I-domain containing a variable domain having a non-human CDR incorporated into a V.sub.H subgroup III consensus human antibody variable domain, and further comprising an amino acid substitution at a site selected from the group consisting of 27H, 28H, 30H, 49H, 71H and 73H.

27. The humanized anti-CD11a antibody of claim 26, having at least one of the following properties: (a) binds human CD11a with a K.sub.d value of no more than about 1.times.10.sup.-8 M, (b) has an IC50 (nM) value of no more than about 1 nM for preventing adhesion of Jurkat cells to normal human epidermal keratinocytes expressing ICAM-1, or (c) has an IC50 (nM) value of no more than about 1 nM in a mixed lymphocyte response assay.

28. The humanized anti-CD11a antibody of claim 26, having human kappa I consensus light chain framework residue 66L.

29. The humanized anti-CD11a antibody of claim 26, having all human kappa I consensus light chain framework residues.

30. The humanized anti-CD11a antibody of claim 26, having human V.sub.H subgroup III consensus heavy chain framework residue 93H.

L17 ANSWER 32 OF 54 USPATFULL
1999:159484 Method of using humanized antibody against CD18.
Waldmann, Herman, 4 Apsley Road, Oxford, United Kingdom OX2 7QY
Sims, Martin J., 29 Hines Lane, Comberton, Cambridge, United Kingdom CB3 7BZ
Crowe, J. Scott, 25 Earlsmead, Letchworth, Herts. SG6 3UE, United Kingdom
US 5997867 19991207
APPLICATION: US 1995-465313 19950605 (8)
PRIORITY: GB 1991-15364 19910716
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Methods of treating patients suffering from, or at risk of developing, a leukocyte mediated disease comprising the administration of humanized antibodies and fragments thereof that bind human CD18 are disclosed.
CLM What is claimed is:
1. A method for treating a patient suffering from, or at risk of developing, a leukocyte mediated disease comprising administering to the patient a therapeutically or prophylactically effective amount, respectively, of a humanized antibody or fragment thereof wherein said antibody or fragment specifically binds to human CD18 antigen, and the complementarity determining regions (CDR1, CDR2 and CDR3) of the light chain variable region of said antibody or fragment and the complementarity determining regions (CDR1, CDR2 and CDR3) of the heavy chain variable region of said antibody or fragment have the following amino acid sequences:
light chain: CDR1 (SEQ ID NO: 4)
CDR2 (SEQ ID NO: 6)
CDR3 (SEQ ID NO: 8)
heavy chain: CDR1 (SEQ ID NO: 12)

CDR2 (SEQ ID NO: 14)
CDR3 (SEQ ID NO: 16).

2. A method in accordance with claim 1, wherein the humanized antibody or fragment can compete with a rat antibody for binding to CD18+ T cells, said rat antibody comprising the light chain variable region of SEQ ID NO:2 and the heavy chain variable region of SEQ ID NO:10.

3. A method in accordance with claim 1, wherein the leukocyte mediated disease comprises adult respiratory distress syndrome, asthma or leukocyte-mediated reperfusion damage.

4. A method in accordance with claim 1, wherein the leukocyte mediated disease comprises leukocyte-mediated reperfusion damage.

5. A method in accordance with claim 1, wherein the leukocyte mediated disease comprises leukocyte-mediated reperfusion damage post thrombolytic therapy.

6. A method in accordance with claim 1, wherein said antibody or fragment is administered to eliminate or reduce organ inflammation caused by non-infectious trauma.

7. A method in accordance with claim 1, wherein said antibody or fragment is administered to reduce or eliminate inflammation in a patient being treated with an anti-infective agent.

8. A method in accordance with claim 1, wherein said antibody or fragment is administered in combination with an additional agent, wherein said additional agent comprises a therapeutic agent.

9. A method in accordance with claim 8, wherein the additional therapeutic agent comprises an antibody, a chemotherapeutic agent or an immunosuppressive agent.

10. A method in accordance with claim 1, wherein the antibody or fragment is administered in combination with a cytotoxic agent.

11. A method in accordance with claim 10, wherein the cytotoxic agent comprises a radionuclide, a chemotherapeutic agent or a cytotoxic protein.

12. A method in accordance with claim 1, wherein the antibody or fragment is in a form suitable for parenteral administration.

13. A method in accordance with claim 1, wherein the antibody or fragment is administered in a therapeutic daily dose of about 1 to about 200 mg antibody.

14. A method in accordance with claim 13, wherein the antibody or fragment is administered in a daily dose of 5 to 25 mg antibody.

15. A method in accordance with claim 1, wherein the antibody or fragment is administered in a prophylactic daily dose of about 0.1 to 25 mg.

16. A method in accordance with claim 1, wherein the antibody or fragment is administered in a daily dose of 0.5 to 2.5 mg.

17. A method for treating a patient suffering from, or at risk of developing, a leukocyte-mediated disease characterized by leukocyte ingress comprising administering to the patient a therapeutically or prophylactically effective amount, respectively, of a humanized antibody or fragment thereof wherein said antibody or fragment specifically binds to human CD18 antigen, and the complementarity determining regions (CDR1, CDR2 and CDR3) of the light chain variable region of said antibody or fragment and the complementarity determining regions (CDR1, CDR2 and CDR3) of the heavy chain variable region of said antibody or fragment have the following amino acid sequences: light chain: CDR1 (SEQ ID NO: 4)
CDR2 (SEQ ID NO: 6)
CDR3 (SEQ ID NO: 8)
heavy chain: CDR1 (SEQ ID NO: 12)
CDR2 (SEQ ID NO: 14)
CDR3 (SEQ ID NO: 16).

18. A method according to claim 17 wherein the humanized antibody or fragment thereof can compete with a rat antibody for binding to CD18+ T cells, said rat antibody comprising the light chain variable region of SEQ ID NO:2 and the heavy chain variable region of SEQ ID NO:10.

L17 ANSWER 33 OF 54 USPATFULL
1999:145979 Humanized antibody against CD18.
Waldmann, Herman, University of Cambridge, Department of Pathology Tennis Court Road, Cambridge, United Kingdom CB2 1QP
Sims, Martin, The Wellcome Foundation Limited Langley Court, Beckenham, United Kingdom
Crowe, Scott, The Wellcome Foundation Limited Langley Court, Beckenham, United Kingdom BR3 3BS
US 5985279 19991116
WO 9302191 19930204
APPLICATION: US 1994-182067 19940323 (8)
WO 1992-GB1289 19920715 19940323 PCT 371 date 19940323 PCT 102(e) date
PRIORITY: GB 1991-15364 19910716
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Humanized antibodies and fragments thereof that bind human CD18 are disclosed. Nucleic acids encoding anti-CD18 antibodies or fragments thereof, as well as expression vectors and host cells incorporating these nucleic acids for the recombinant expression of anti-CD18 antibodies are also encompassed by the invention. Pharmaceutical compositions comprising the antibodies of the invention are also disclosed.
CLM What is claimed is:
1. A humanised antibody or fragment thereof wherein said antibody or fragment specifically binds to human CD18 antigen, wherein the complementarity determining regions (CDR1, CDR2 and CDR3) of the light chain variable region and the complementarity determining regions (CDR1, CDR2 and CDR3) of the heavy chain variable region have the following amino acid sequences: light chain: CDR1 (SEQ ID NO: 4) CDR2 (SEQ ID NO: 6) CDR3 (SEQ ID NO: 8) heavy chain: CDR1 (SEQ ID NO: 12) CDR2 (SEQ ID NO: 14) CDR3 (SEQ ID NO: 16).

2. An antibody or fragment as claimed in claim 1, in which the variable domain framework of the light chain is the light chain variable domain framework of the protein REI.

3. An antibody or fragment as claimed in claim 1, in which the variable domain framework of the heavy chain is the heavy chain variable domain framework of the protein NEWM.

4. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and, as active ingredient, a humanised antibody or fragment as defined in claim 1.

5. A DNA molecule encoding the amino acid sequence of a humanised antibody or fragment thereof wherein said antibody or fragment specifically binds to human CD18 antigen, wherein the CDRs of the light chain variable region and the CDRs of the heavy chain variable region have the following amino acid sequences: light chain: CDR1 (SEQ ID NO: 4) CDR2 (SEQ ID NO: 6) CDR3 (SEQ ID NO: 8) heavy chain: CDR1 (SEQ ID NO: 12) CDR2 (SEQ ID NO: 14) CDR3 (SEQ ID NO: 16).

6. A DNA molecule as claimed in claim 5, in which the variable domain framework of the light chain is the light chain variable domain framework of the protein REI.

7. A DNA molecule as claimed in claim 5, in which the variable domain framework of the heavy chain is the heavy chain variable domain framework of the protein NEWM.

8. A DNA molecule encoding the light chain of an antibody or fragment as claimed in claim 1.

9. A DNA molecule as claimed in claim 8, wherein the nucleotide sequences of the light chain CDRs are as follows: CDR1 (SEQ ID NO: 3) CDR2 (SEQ ID NO: 5) CDR3 (SEQ ID NO: 7).

10. A DNA molecule encoding the heavy chain of an antibody or fragment as claimed in claim 1.

11. A DNA molecule as claimed in claim 10, wherein the nucleotide sequences of the heavy chain CDRs are as follows: CDR1 (SEQ ID NO: 11) CDR2 (SEQ ID NO: 13) CDR3 (SEQ ID NO: 15).

12. A DNA molecule as claimed in claim 5, 6, or 7 in the form of an expression vector.

13. A host transformed with an expression vector as claimed in claim 12.

14. A host cell comprising a recombinant expression system encoding the light and heavy chains of an antibody or fragment of claim 1.

15. A process for the preparation of a humanised antibody or fragment as defined in claim 1, 2 or 3, which process comprises providing a host transformed with either (i) a first expression vector which encodes the light chain of the humanised antibody or fragment and a second expression vector which encodes the heavy chain of the humanised antibody or fragment; or (ii) a single expression vector which encodes both the light chain and the heavy chain of the humanised antibody or fragment; and maintaining said host under such conditions that each chain is expressed and isolating the humanised antibody or fragment formed by assembly of the thus-expressed chains.

16. A method for producing a humanised antibody or fragment thereof which specifically binds to human CD18 antigen,

wherein said antibody or fragment comprises the variable region of a light chain and the variable region of a heavy chain, and the complementarity determining regions (CDRs) have the following amino acid sequences: light chain: CDR1 (SEQ ID NO: 4) CDR2 (SEQ ID NO: 6) CDR3 (SEQ ID NO: 8) heavy chain: CDR1 (SEQ ID NO: 12) CDR2 (SEQ ID NO: 14) CDR3 (SEQ ID NO: 16), said method comprising culturing a host cell, wherein said host cell comprises a recombinant expression system encoding the light and heavy chains of said antibody or fragment, and recovering said antibody or fragment.

17. A humanized antibody or fragment thercof which specifically binds to human CD18 antigen wherein the complementarity determining regions (CDRs) have the following amino acid sequences: light chain: CDR1 (SEQ ID NO: 4) CDR2 (SEQ ID NO: 6) CDR3 (SEQ ID NO: 8) heavy chain: CDR1 (SEQ ID NO: 12) CDR2 (SEQ ID NO: 14) CDR3 (SEQ ID NO: 16), and wherein the variable domain framework of the light chain is derived from the variable domain framework of the protein REI and the variable domain framework of the heavy chain is derived from the variable domain framework of the protein NEWM.

18. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and, as active ingredient, a humanised antibody or fragment as defined in claim 17.

19. A DNA molecule encoding the light chain of an antibody or fragment of claim 17.

20. A DNA molecule encoding the heavy chain of an antibody or fragment of claim 17.

21. A host cell comprising a recombinant expression system encoding the light and heavy chains of an antibody or fragment of claim 17.

22. A method for producing a humanized antibody or fragment thereof, comprising culturing a host cell of claim 21, and recovering said antibody or fragment.

23. A humanised antibody or fragment thereof wherein said antibody or fragment specifically binds to human CD18 antigen, wherein the complementarity determining regions (CDR1, CDR2 and CDR3) of the light chain variable region and the complementarity determining regions (CDR1, CDR2 and CDR3) of the heavy chain variable region have the following amino acid sequences and wherein the antibody or fragment can compete with rat YFC 51.1 for binding to CD18.sup.+ cells: light chain: CDR1 (SEQ ID NO: 4) CDR2 (SEQ ID NO: 6) CDR3 (SEQ ID NO: 8) heavy chain: CDR1 (SEQ ID NO: 12) CDR2 (SEQ ID NO: 14) CDR3 (SEQ ID NO: 16).

24. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and, as active ingredient, a humanised antibody or fragment as defined in claim 23.

25. A DNA molecule encoding the light chain of an antibody or fragment of claim 23.

26. A DNA molecule encoding the heavy chain of an antibody or fragment of claim 23.

27. A host cell comprising a recombinant expression system encoding the light and heavy chains of an antibody or fragment of claim 23.

28. A method for producing a humanized antibody or fragment thereof, comprising culturing a host cell of claim 27, and recovering said antibody or fragment.

L17 ANSWER 35 OF 54 USPATFULL
1999:69502 Anti-CD18 antibodies in stroke.
Bednar, Martin M., South Burlington, VT, United States
Gross, Cordell E., Williston, VT, United States
Thomas, G. Roger, Burlingame, CA, United States
Genentech, Inc., South San Francisco, CA, United States (U.S. corporation)Univ. of VT and State Agricultural College, Burlington, VT, United States (U.S. corporation)
US 5914112 19990622
APPLICATION: US 1997-788800 19970122 (8)
PRIORITY: US 1996-93038P 19960123 (60)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method for improving clinical outcome in focal ischemic stroke in a mammal by increasing cerebral blood flow and/or reducing infarct size is described which involves administering an effective amount of an anti-CD18 antibody to the mammal, in the absence of removal of the arterial obstruction.
CLM What is claimed is:
1. A method for treating focal ischemic stroke caused by obstruction of a main cerebral artery in a human mammal comprising administering an amount of an anti-CD18 antibody to the mammal which is effective for increasing cerebral blood flow or reducing infarct size, in the absence of removal of the arterial obstruction, wherein at least one of the following conditions is present: (a) the antibody binds to an extracellular domain of CD18 and inhibits or reduces the ability of a cell expressing CD18 to bind to endothelium, (b) the antibody binds CD18 with an affinity of 4 nm or less, or (c) the antibody dissociates a CD11b/CD18 complex.

2. The method of claim 1 which increases cerebral blood flow and reduces infarct size in the mammal.

3. The method of claim 1 wherein the anti-CD18 antibody fragment.

4. The method of claim 3 wherein the anti-CD18 antibody fragment is a F(ab').sub.2.

5. The method of claim 1 wherein the anti-CD18 antibody is humanized.

6. The method of claim 1 wherein the anti-CD18 antibody is administered to the mammal by bolus dosage.

7. The method of claim 1 wherein the anti-CD18 antibody is administered intravenously.

8. The method of claim 1 wherein the anti-CD18 antibody is administered via continuous infusion.

9. The method of claim 1 wherein the anti-CD18 antibody is administered to the mammal at a time between about 15 minutes to about 20 hours from the onset of focal ischemic stroke.

10. The method of claim 9 wherein the anti-CD18 antibody is administered to the mammal at a time between about 45 minutes to about 5 hours from the onset of focal ischemic stroke.

11. The method of claim 1 wherein the anti-CD18 antibody is humanized H52 antibody comprising heavy chain sequence of SEQ ID NO:10 and light chain sequence of SEQ ID NO:11.

12. The method of claim 11 wherein the H52 antibody is a F(ab').sub.2.

13. The method of claim 1, wherein the anti-CD18 antibody binds to an extracellular domain of CD18 and inhibits or reduces the ability of a cell expressing CD18 to bind to endothelium.

14. The method of claim 1, wherein the anti-CD18 antibody binds CD18 with an affinity of 4 nm or less.

15. The method of claim 1, wherein the anti-CD18 antibody binds CD18 with an affinity of 3 nm or less.

16. The method of claim 1, wherein the anti-CD18 antibody binds CD18 with an affinity of 1 nm or less.

17. The method of claim 1, wherein the anti-CD18 antibody dissociates the CD11b/CD18 complex.

18. The method of claim 1, wherein the anti-CD18 antibody binds to the epitope bound by H52 antibody.

L17 ANSWER 42 OF 54 USPATFULL
1998:51191 Recombinant antibodies for human therapy.
Newman, Roland A., San Diego, CA, United States
Hanna, Nabil, Olivenhain, CA, United States
Raab, Ronald W., San Diego, CA, United States
IDEC Pharmaceuticals Corporation, San Diego, CA, United States (U.S. corporation)
US 5750105 19980512
APPLICATION: US 1995-476349 19950607 (8)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Chimeric antibodies including an Old World monkey portion and a human portion, nucleic acid encoding such antibodies, Old World monkey monoclonal antibodies, and methods for their production and use.
CLM What is claimed is:
1. An improved method for treatment of a subject which comprises the administration of an antibody to a subject in need for such treatment, wherein the improvement comprises the administration of a therapeutically or prophylactically effective amount of an antibody which comprises an Old World monkey variable region which binds to an antigen, or antigen-binding portion thereof, and a human constant domain.

2. The method of claim 1, wherein said antibody binds to a tumor antigen and the treatment comprises treatment of cancer.

3. The method of claim 1, wherein said antibody binds to an antigen involved in autoimmune response and the treatment comprises

treatment of an autoimmune disorder.

4. The method of claim 1, wherein said antibody binds to an antigen wherein said antigen is a receptor expressed by a cell of the treated subject.

5. The method of claim 1, wherein said antigen is selected from the group consisting of CD58, VCAM, VLA4, CD2, LFA3, ELAM, LAM, CD25, CD4, CD19, CD20, CD23, CD41, CD44, CD54, TNF.alpha., TNF.beta., Tn antigen, IL-1, IL-8, human T-cell receptor, CD3, CD28, CD8, CD18, CD11a, CD11b, CD11c, CD5a, CD45, neu oncogene product, MDR-1, TGF.alpha., TGF.alpha.-receptor, PDGF, and CD71.

6. The method of claim 1, wherein said antigen-binding portion comprises one or more CDR regions of an Old World monkey variable region.

7. The method of claim 1, wherein said antibody comprises an entire variable region of an Old World monkey antibody.

8. The method of claim 1, wherein the treatment comprises treatment of a disease selected from the group consisting of rheumatoid arthritis, eczema, and immuno-modulated diseases, and the antigen bound by the antibody is CD4.

9. The method of claim 8, wherein the antibody comprises the variable domain sequence as set forth in Sequence ID NO. 108 or Sequence ID NO. 110.

10. The method of claim 9, wherein the therapy is for the treatment of rheumatoid arthritis.

L17 ANSWER 49 OF 54 USPATFULL
97:33495 Method for treating a LFA-1-mediated disorder.
Jardieu, Paula M., Berkeley, CA, United States
Montgomery, Bruce, Redwood City, CA, United States
Genentech, Inc., South San Francisco, CA, United States (U.S. corporation)
US 5622700 19970422
APPLICATION: US 1995-432543 19950502 (8)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method is provided for administering to a mammal suffering from, or at risk for, a LFA-1-mediated disorder an initial dosing of a therapeutically effective amount of LFA-1 antagonist, followed by a subsequent intermittent dosing of a therapeutically effective amount of LFA-1 antagonist that is less than 100%, calculated on a daily basis, of the initial dosing of antagonist.
CLM What is claimed is:
1. A method for treating psoriasis in a mammal without depleting T-lymphocytes in the mammal comprising administering to the mammal an initial dosing of a therapeutically effective amount of an anti-LFA-1 antibody or an anti-ICAM-1 antibody, followed by a subsequent intermittent dosing of a therapeutically effective amount of the antibody that is less than 100%, calculated on a daily basis, of the initial dosing of the abtibody, wherein the antibody is administered to the mammal not more than once per week during the subsequent dosing.

2. The method of claim 1 wherein the subsequent dosing is less than about 50%, calculated on a daily basis, of the initial dosing of the antibody.

3. The method of claim 1 wherein the subsequent dosing is less than about 25%, calculated on a daily basis, of the initial dosing of the antibody.

4. The method of claim 1 wherein the subsequent dosing is less than about 10%, calculated on a daily basis, of the initial dosing of the antibody.

5. The method of claim 1 wherein the subsequent dosing is less than about 2%, calculated on a daily basis, of the initial dosing of the antibody.

6. The method of claim 1 further comprising administering an effective amount of an immunosuppressive agent to the mammal.

7. The method of claim 1 further comprising administering an effective amount of cyclosporin A to the mammal.

8. The method of claim 1 wherein the mammal is a human.

9. The method of claim I wherein the subsequent dosing is carried out for a longer time than the initial dosing.

10. The method of claim 6 wherein the initial dosing consists of daily administration.

11. The method of claim 1 wherein the subsequent dosing comprises administration of the antibody no more than once biweekly for at least about 5 weeks after the end of the initial dosing.

12. The method of claim 1 wherein the dosing is given by intravenous or subcutaneous injections.

13. The method of claim 1 wherein the antibody is an anti-LFA-1 antibody.

14. The method of claim 13 wherein the antibody is an anti-CD11a or anti-CD18 antibody.

15. The method of claim 13 wherein the antibody is an anti-CD11a antibody.

16. The method of claim 1 wherein the antibody is an anti-ICAM-1 antibody.

17. The method of claim 1 wherein the subsequent dosing is administered to the mammal for at least about 5 weeks after the initial dosing is terminated.

18. The method of claim 1 wherein the subsequent dosing is administered to the mammal for at least about 10 weeks after the initial dosing is terminated.

19. A method for prolonging survival of a transplanted graft in a mammalian host for greater than 200 days comprising administering to the mammalian host an initial dosing of a therapeutically effective amount of anti-LFA-1 antibody, followed by a subsequent intermittent dosing of a therapeutically effective amount of anti-LFA-1 antibody that is less than 100%, calculated on a daily basis, of the initial dosing of anti-LFA-1 antibody, wherein the

subsequent intermittent dosing comprises administration of anti-LFA-1 antibody no more than once per week for at least about 10 weeks after the initial dosing is terminated, T lymphocytes are not depleted in the mammalian host, and the method results in specific immunosuppression.

20. The method of claim 19 wherein the anti-LFA-1 antibody is an anti-CD11a antibody or an anti-CD18 antibody.

21. The method of claim 20 wherein the anti-LFA-1 antibody is an anti-CD11a antibody.

22. The method of claim 19 wherein the subsequent dosing is less than about 50%, calculated on a daily basis, of the initial dosing of anti-LFA-1 antibody.

23. The method of claim 19 wherein the subsequent dosing is less than about 25%, calculated on a daily basis, of the initial dosing of anti-LFA-1 antibody.

24. The method of claim 19 wherein the subsequent dosing is less than about 10%, calculated on a daily basis, of the initial dosing of anti-LFA-1 antibody.

25. The method of claim 19 wherein the subsequent dosing is less than about 2%, calculated on a daily basis, of the initial dosing of anti-LFA-1 antibody.

26. The method of claim 19 wherein the initial dosing takes place before, during, and after transplantation has occurred.

27. The method of claim 19 further comprising administering an effective amount of an immunosuppressive agent to the mammal.

28. The method of claim 19 further comprising administering an effective amount of cyclosporin A to the mammal.

29. The method of claim 19 wherein the mammal is a human.

30. The method of claim 29 wherein the donor of the graft and the recipient are matched for HLA class II antigens.

31. The method of claim 19 wherein the subsequent dosing is carried out for a longer time than the initial dosing.

32. The method of claim 19 wherein the initial dosing consists of daily administration.

33. The method of claim 19 wherein the subsequent dosing comprises administration of anti-LFA-1 antibody no more than once biweekly.

34. The method of claim 19 wherein the initial dosing terminates from about 1 day to 4 weeks after transplantation has occurred and commences from about 1 week before transplantation occurs up to about simultaneously with the transplantation.

35. The method of claim 19 wherein the dosing is given by intravenous or subcutaneous injections.

36. A method for prolonging survival of a transplanted graft in a mammal without depleting T-lymphocytes in the mammal comprising administering to the mammal an initial dosing of a therapeutically effective amount of an anti-LFA-1 antibody or an anti-ICAM-1 antibody, followed by a subsequent intermittent dosing of a therapeutically effective amount of the antibody that is less than 100%, calculated on a daily basis, of the initial dosing of the antibody, wherein the antibody is administered to the mammal not more than once per week during the subsequent dosing.

37. The method of claim 36 wherein the antibody administered to the mammal is an anti-LFA-1 antibody.

L36 ANSWER 7 OF 7 MEDLINE
89266919 Document Number: 89266919. PubMed ID: 2543075. Involvement of a leukocyte adhesion receptor (LFA-1) in HIV -induced syncytium formation. Hildreth J E; Orentas R J. (Department of Pharmacology and Molecular Sciences, Johns Hopkins University School of Medicine, Baltimore, MD 21205.) SCIENCE, (1989 Jun 2) 244 (4908) 1075-8. Journal code: 0404511. ISSN: 0036-8075. Pub. country: United States. Language: English.
AB Cell fusion (syncytium formation) is a major cytopathic effect of infection by human immunodeficiency virus (HIV) and may also represent an important mechanism of CD4+ T-cell depletion in individuals infected with HIV. Syncytium formation requires the interaction of CD4 on the surface of uninfected cells with HIV envelope glycoprotein gp120 expressed on HIV-infected cells. However, several observations suggest that molecules other than CD4 play a role in HIV-induced cell fusion. The leukocyte adhesion receptor LFA-1 is involved in a broad range of leukocyte interactions mediated by diverse receptor-ligand systems including CD4-class II major histocompatibility complex (MHC) molecules. Possible mimicry of class II MHC molecules by gp120 in its interaction with CD4 prompted an examination of the role of LFA-1 in HIV-induced cell fusion. A monoclonal antibody against LFA-1 completely inhibited HIV-induced syncytium formation. The antibody did not block binding of gp120 to CD4. This demonstrates that a molecule other than CD4 is also involved in cell fusion mediated by HIV.

L36 ANSWER 6 OF 7 MEDLINE
93305386 Document Number: 93305386. PubMed ID: 8100439. Regulation of HIV production by blood mononuclear cells from HIV -infected donors: II. HIV-1 production depends on T cell-monocyte interaction. Diegel M L; Moran P A; Gilliland L K; Damle N K; Hayden M S; Zarling J M; Ledbetter J A. (Bristol-Myers Squibb Pharmaceutical Research Institute, Seattle, WA 98121.) AIDS RESEARCH AND HUMAN RETROVIRUSES, (1993 May) 9 (5) 465-73. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.
AB Cell-cell interactions induced between T cells and monocytes by certain soluble anti-CD3 monoclonal antibodies (MAbs) were previously shown to be required for high-level production of HIV -1 by peripheral blood mononuclear cells (PBMCs) from infected donors. Staphylococcal enterotoxin or superantigen (SAg) is another mitogen inducing monocytes-T cell interactions that exhibit potent induction of HIV-1 production. Antibodies to several adhesion molecules were used to test the requirements for T cell- and monocyte-associated adhesion molecules in HIV-1 production following activation with anti-CD3 or SAg. Blocking of either CD2-LFA-3, or CD18-ICAM-1, inhibited anti-CD3- or SAg-induced HIV-1 production by more than 90% without inhibiting CD4+ T cell proliferation. Inhibition of HIV production was observed when either the T cell or monocyte coreceptor was bound by MAbs to these adhesion molecules. Blocking of CD28-B7 interactions by soluble CTLA-4 fusion protein, a CD28 homolog, inhibited both HIV-1 production and CD4+ T cell proliferation. Fc binding was not required for HIV-1 inhibition by MAbs to CD2 and CD18, because Fab or F(ab')2 fragments of these MAbs inhibited HIV-1 production by more than 80%. A chimeric single-chain MAb to CD2 was produced, containing heavy and light chain variable regions from MAb 35.1 to CD2 linked to the constant regions of human IgG1 (CD2 SFv-Ig). This humanized CD2 SFv-Ig inhibited

HIV-1 production by 30% to > 98%. These results thus indicate that simultaneous engagement of multiple adhesion pathways between T cells and monocytes are required for HIV production by patients PBMCs and may have implications for therapy of HIV infections.

L36 ANSWER 5 OF 7 MEDLINE
95000931 Document Number: 95000931. PubMed ID: 7917519. Adhesion mediated by intercellular adhesion molecule 1 attenuates the potency of antibodies that block HIV-1 gp160-dependent syncytium formation.
Berman P W; Nakamura G R. (Department of Immunology, Genentech, Inc., South San Francisco, California 94080.) AIDS RESEARCH AND HUMAN RETROVIRUSES, (1994 May) 10 (5) 585-93. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.
AB Several lines of evidence suggest that leukocyte adhesion molecules can promote HIV-1-mediated cell fusion and syncytium formation. In the present studies, the human kidney cell line, 293, was transfected with the envelope glycoprotein gene of the MN strain of HIV-1 alone or cotransfected with a cDNA encoding intercellular adhesion molecule 1 (ICAM-1). It was found that 293 cells transfected with the HIV-1MN env gene expressed the HIV-1 polyglycoprotein precursor, gp160, and the mature gp120-gp41 complex. When mixed with a CD4+ T cell line (CEM), the gp160-transfected cells mediated heterotypic cell fusion and formed multinucleate syncytia. Virus-neutralizing monoclonal antibodies to the V2 and V3 domains of gp120 were able to inhibit syncytium formation, as were monoclonal antibodies to CD4. When ICAM-1 was coexpressed with gp160, syncytium formation between the transfected kidney cells and uninfected CD$+ T cells was markedly enhanced. Inhibitors of HIV-1 infectivity (e.g., monoclonal antibodies to gp120, recombinant soluble CD4) were able to prevent syncytium formation; however, the syncytium-blocking activity of these agents was significantly attenuated in cultures in which ICAM-1 was cotransfected with gp160. These results confirm that leukocyte adhesion molecules can promote gp160-mediated syncytium formation and demonstrate, for the first time, that adhesive interactions mediated by ICAM-1 and its contrareceptor, LFA-1, attenuate the syncytium-inhibiting activity of virus-neutralizing monoclonal antibodies and soluble CD4. These findings suggest that the type and magnitude of leukocyte adhesion molecules expressed on cells may be a significant variable in in vitro HIV-1 neutralization assays.

L36 ANSWER 4 OF 7 MEDLINE
95302030 Document Number: 95302030. PubMed ID: 7540195. Intercellular adhesion molecule 3, a candidate human immunodeficiency virus type 1 co-receptor on lymphoid and monocytoid cells.
Sommerfelt M A; Asjo B. (Centre for Research in Virology, University of Bergen, Bergen High Technology Centre, Norway.) JOURNAL OF GENERAL VIROLOGY, (1995 Jun) 76 (Pt 6) 1345-52. Journal code: 0077340. ISSN: 0022-1317. Pub. country: ENGLAND: United Kingdom. Language: English.
AB The CD4 molecule serves as the principal cell surface receptor common to both the human and simian immunodeficiency viruses (HIV-1, HIV-2 and SIV). Since binding to CD4 is not sufficient to permit virus entry, HIV 'co-receptors' have been implicated in mediating the fusion of viral and cellular membranes necessary for completing the entry process. In order to identify candidate co-receptor molecules, a panel of monoclonal antibodies (MAbs) directed against adhesion molecules was tested for the ability of the MAbs to inhibit HIV-1-induced cell fusion (syncytium formation) and HIV-1 entry. Certain antibodies directed against CD18, CD11b and CD11c inhibited

HIV-1-induced syncytium formation but not entry, in agreement with previous reports. Interestingly, certain antibodies to ICAM-3 (intercellular adhesion molecule 3) (CD50) significantly inhibited HIV-1-specific entry but not syncytium formation using human SupT1 cells. Only one antibody directed against ICAM-3 significantly inhibited HIV-1-induced syncytium formation, entry and infectivity. Our results suggest that certain epitopes of ICAM-3 may be involved in mediating HIV-1-specific entry into lymphoid and monocytoid cells.

L36 ANSWER 3 OF 7 MEDLINE

1999030116 Document Number: 99030116. PubMed ID: 9814951. Role of cellular adhesion molecules in HIV type 1 infection and their impact on virus neutralization. Hioe C E; Bastiani L; Hildreth J E; Zolla-Pazner S. (Department of Pathology, New York University Medical Center, New York 10010, USA.) AIDS RESEARCH AND HUMAN RETROVIRUSES, (1998 Oct) 14 Suppl 3 S247-54. Ref: 69. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.

AB While CD4 and several chemokine receptors are the principal receptors for human immunodeficiency virus type 1 (HIV-1) viruses, other cell membrane proteins also play a role in HIV-1 infection. A large array of host cell-derived membrane proteins, including adhesion molecules, are incorporated into the envelope of HIV-1 virions, and the profile of host cell proteins acquired by the virus depends on the cells used to propagate the virus. The major leukocyte adhesion molecules, such as leukocyte-function associated antigen-1 (LFA-1), intercellular adhesion molecule-1 (ICAM-1), and CD44, retain their biological functions when expressed on the virion surface, and have been shown to increase virus-cell interaction, enhance virus infectivity, and extend the host cell range of the virus. LFA-1 and its ICAM ligands are also necessary for syncytium formation and cell-to-cell transmission of HIV-1. Furthermore, several studies demonstrate that the presence and level of cell-derived adhesion molecules on the surface of HIV -1 virions affect the process by which antibody-mediated virus neutralization occurs and is measured: the level of virus neutralization is influenced by the host cell-derived adhesion molecules present on the virus, and thus, by the type of host cells in which the virus was produced. Adhesion molecules expressed on the target cells used in neutralization assays similarly affect HIV -1 neutralization by virus-specific antibodies. Consistent with these observations is the finding that neutralizing activities of both HIV+ plasma and human anti-gp120 monoclonal antibodies (Mabs) are enhanced by an anti-LFA-1 Mab capable of blocking LFA-1 functions. Hence, LFA-1, ICAM-1, and other cellular adhesion molecules are involved in different stages of HIV-1 infection and profoundly affect HIV-1 neutralization by virus-specific antibodies. These findings illuminate the biology of virus-cell interactions and have significant implications for evaluating candidate HIV vaccines.

L41 ANSWER 19 OF 20 MEDLINE
92032833 Document Number: 92032833. PubMed ID: 2131019. Regulatory agency concerns in the manufacturing and testing of monoclonal antibodies for therapeutic use. Baker D A; Harkonen W S. (Bio Response, Inc., Hayward, California.) TARGETED DIAGNOSIS AND THERAPY, (1990) 3 75-98. Ref: 21. Journal code: 8913519. ISSN: 1046-1906. Pub. country: United States. Language: English.
AB Monoclonal antibody-based therapeutic products are subject to the same regulatory review procedures and submissions requirements as more traditional pharmaceutical agents. In addition, the FDA often asks for specific information on the unique aspects of the manufacture, characterization, and testing of these products. Agency concern begins with the origin of the hybridoma cell line and continues through preclinical safety testing and clinical trials. Specific regulatory issues are often decided on a case-by-case basis with the FDA reviewers. Implementing an effective strategy for identifying and addressing these issues and concerns is a critical part of the development process.

L41 ANSWER 18 OF 20 MEDLINE
93162703 Document Number: 93162703. PubMed ID: 1286872. Engineering antibodies for therapy. Adair J R. (Celltech Research Division, Celltech Ltd, Slough Berks, U.K.) IMMUNOLOGICAL REVIEWS, (1992 Dec) 130 5-40. Ref: 171. Journal code: 7702118. ISSN: 0105-2896. Pub. country: Denmark. Language: English.
AB Success in the generation of an antibody-based therapeutic requires careful consideration of the binding site, to achieve specificity and high affinity; of the effector, to produce the desired therapeutic effect; of the means of attachment of the effector to the binding site; production of the end product; and the response made by the patient to the administered compound. Each of these areas is receiving attention by antibody-engineering techniques. The number of potentially useful monoclonal antibodies developed over the last 10 years, and currently in clinical trials or preregistration, is now being increased by these engineered newcomers. It will be interesting to see over the next few years how many of these antibodies, and of which kind, emerge as products.

L41 ANSWER 17 OF 20 MEDLINE
94162650 Document Number: 94162650. PubMed ID: 7764499. Antibody -based therapeutics--the third generation. Sleigh M. (Peptide Technology Limited, N.S.W.) AUSTRALASIAN BIOTECHNOLOGY, (1993 Nov-Dec) 3 (6) 328-31. Ref: 6. Journal code: 9113681. ISSN: 1036-7128. Pub. country: Australia. Language: English.
AB Peptide Technology Limited (Peptech) recently announced in Australia that its associate company, Cambridge Antibody Technology (CAT) had obtained rights to the commercial development of a new kind of engineered antibody molecule. Diabodies were pioneered by Dr Greg Winter of the Medical Research Council Laboratories in Cambridge. In this article, the origins and potential of diabodies are examined in the context of other recent developments in this very fast moving field.

L41 ANSWER 14 OF 20 MEDLINE
95391276 Document Number: 95391276. PubMed ID: 7662305. Clinical issues in antibody design. Chester K A; Hawkins R E. (Department of Clinical Oncology, Royal Free Hospital School of Medicine, London, UK.) TRENDS IN BIOTECHNOLOGY, (1995 Aug) 13 (8) 294-300. Ref: 54. Journal code: 8310903. ISSN: 0167-7799. Pub. country: ENGLAND: United Kingdom. Language: English.
AB Antibody genes can now be cloned and expressed in various ways to give new versions of antibodies that possess reduced immunogenicity, improved

affinity, altered size, increased avidity and novel effector functions. The task for any clinical application is, first, to define a relevant target, and then to design the optimal antibody-based therapeutic molecule to react with that target. This article reviews these improved antibody-based molecules and examines their role in cancer therapy.

L41 ANSWER 5 OF 20 MEDLINE
2001293974 Document Number: 21271103. PubMed ID: 11378956. Therapeutic antibody production technologies: molecules, applications, expression and purification. Humphreys D P; Glover D J. (Celitech-Chiroscience Ltd, 216 Bath Road, Slough, Berkshire SL1 4EN, UK.. dhumphre@celitech.co.uk) . Curr Opin Drug Discov Devel, (2001 Mar) 4 (2) 172-85. Ref: 217. Journal code: 100887519. ISSN: 1367-6733. Pub. country: England: United Kingdom. Language: English.
AB Antibody-based therapeutics are currently being tested in an increasingly diverse range of therapeutic modalities. Many different engineered formats for the antibody molecule and multiple methods for raising and tailoring binding specificities are currently available. Comparison of the relative function and efficacy of these molecules and the many competing methods for their production is crucial for making an informed selection of a new therapeutic entity. In addition, these choices may be influenced by the attached intellectual property burden.

L41 ANSWER 2 OF 20 MEDLINE
2002358746 Document Number: 22096860. PubMed ID: 12102547. Back to the future: antibody-based strategies for the treatment of infectious diseases. Oral H Barbaros; Ozakin Cuneyt; Akdis Cezmi A. (Department of Microbiology and Infectious Diseases, School of Medicine, Uludag University, Bursa, Turkey.. oralb@uludag.edu.tr) . MOLECULAR BIOTECHNOLOGY, (2002 Jul) 21 (3) 225-39. Journal code: 9423533. ISSN: 1073-6085. Pub. country: United States. Language: English.
AB Before antibiotics, sera from immune animals and humans were used to treat a variety of infectious diseases, often with successful results. After the discovery of antimicrobial agents, serum therapy for bacterial infections was rapidly forsaken. In the last two decades, problems with treatment of newly emerged, re-emerged, or persistent infectious diseases necessitated researchers to develop new and/or improved antibody-based therapeutic approaches. This article reviews some information on the use of antibodies for the treatment of infectious diseases, with special reference to the most seminal discoveries and current advances as well as available treatment approaches in this field.

L42 ANSWER 26 OF 29 MEDLINE
93020189 Document Number: 93020189. PubMed ID: 1403647. Clonal dominance: cause for a limited and failing immune response to HIV -1 infection and vaccination. Kohler H; Goudsmit J; Nara P. (San Diego Regional Cancer Center, California.) JOURNAL OF ACQUIRED IMMUNE DEFICIENCY SYNDROMES, (1992) 5 (11) 1158-68. Ref: 80. Journal code: 8812597. ISSN: 0894-9255. Pub. country: United States. Language: English.
AB Oligoclonal and monoclonal antibody populations against different HIV-encoded proteins are common in sera from healthy HIV-1-infected individuals. This is especially important when it includes functional antibody repertoires directed at neutralizing cell free virus or inhibiting cell fusion of virus-infected cells. In the host, during the acute viral syndrome following HIV -1 infection, a rapidly replicating, cell-free and genotypically homogeneous viral population is known to arise from the transmitted viral inoculum. Dominant B and possibly T cell clones responsible for both functional and nonfunctional antibodies appear to arise early in

response to this initially homogeneous cell-free viral population heralding seroconversion. During the viremic phase, deposition of cell-free virus as either complement coated or as immune complexes (iccosomes) within the germinal centers results in continued and long-term boosting of primed B cells. This saturation of antigen presenting germinal centers and the presence of limited, immunodominant cross-reactive epitopes on the envelope glycoprotein of the closely-related and immune selected viral quasispecies in the host appear to continue the boosting effect of the primed secondary response. This repertoire freeze appears to be responsible for limiting the recruitment of new uncommitted B cells to other functional epitopes or affinity maturation of B-cell clones to escape variants and the subsequent production and quality of functional antibody against the evolving/selected virus populations. This may include in addition to neutralizing and cell fusion inhibiting antibody, direct complement-fixing and/or NK-directed antibody-dependent cell-mediated antibody as well as various effector, helper, or T cell-mediated activity. In addition to antiviral antibody responses, antibody directed to other invading pathogens or opportunistic organisms may also be clonaly restricted. Antibody facilitating infectivity or blocking effective immunity may also be included in this phenomena and thus be over represented by such a mechanism. AIDS vaccines utilizing the envelope must identify these epitopes to avoid creating clonal dominance and therefore possibly limit the breadth and specificity of a humoral response following infection. Furthermore, immunotherapeutic approaches designed to recruit humoral immune effector function must be able to overcome the dominance of noneffective antibodies and restore a normal polyclonal immune response against HIV. Further research, therefore, into the humoral and cellular dysregulating properties of the HIV-1 envelope is warranted.

L46 ANSWER 15 OF 25 MEDLINE
93229106 Document Number: 93229106. PubMed ID: 8471310. In vivo administration to rhesus monkeys of a CD4-specific monoclonal antibody capable of blocking AIDS virus replication. Reimann K A; Burkly L C; Burrus B; Waite B C; Lord C I; Letvin N L. (New England Regional Primate Research Center, Harvard Medical School, Southborough, Massachusetts 01772.) AIDS RESEARCH AND HUMAN RETROVIRUSES, (1993 Mar) 9 (3) 199-207. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.

AB Monoclonal antibodies (mAbs) specific for CD4 are potent inhibitors of HIV replication in vitro. These agents may be useful prophylactically or in chronic HIV infection if they can be administered without inducing immunosuppression. In the present study, we explored the safety of a CD4-specific murine mAb in rhesus monkeys. The mAb 5A8, which binds to domain 2 of the CD4 molecule, inhibits AIDS virus replication noncompetitively at a postvirus binding step. This antibody, which had a similar affinity for rhesus monkey and human CD4 cells, efficiently inhibited in vitro replication of both HIV-1 and the simian immunodeficiency virus of macaques. A single 3-mg/kg injection of mAb 5A8 into normal rhesus monkeys coated all circulating and lymph node CD4 cells for 4-6 days. CD4 cells were not cleared from circulation nor was the CD4 molecule modulated from the lymphocyte surface. In fact, administration of mAb 5A8 resulted in an approximately one-to twofold increase in absolute number of circulating CD4 cells. Repeated administration in normal rhesus monkeys resulted in CD4 lymphocyte coating with mAbs for > 9 days without CD4 cell clearance or modulation. While coated with mAbs, PBLs of these monkeys retained normal in vitro proliferative responses to mitogens and these animals generated normal humoral responses in vivo to tetanus toxoid. Loss of cell coating with mAbs in normal monkeys corresponded to the appearance of

anti-mouse immunoglobulin antibodies. Thus, administration of certain anti-CD4 mAbs capable of blocking HIV replication can achieve coating of the entire CD4 cell pool in rhesus monkeys without inducing significant cell loss or immunosuppression.

L46 ANSWER 7 OF 25 MEDLINE
1998252382 Document Number: 98252382. PubMed ID: 9591708. Phase I study of a human monoclonal antibody directed against the CD4-binding site of HIV type 1 glycoprotein 120. Cavacini L A; Samore M H; Gambertoglio J; Jackson B; Duval M; Wisnewski A; Hammer S; Koziel C; Trapnell C; Posner M R. (Department of Medicine, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Massachusetts 02215, USA.) AIDS RESEARCH AND HUMAN RETROVIRUSES, (1998 May 1) 14 (7) 545-50. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.
AB A phase I dose escalation study was conducted with the human monoclonal anti-gp120 antibody F105, to evaluate the safety, pharmacokinetics, and functional activity of F105 in HIV-1-infected individuals. F105 is an IgG1(kappa) antibody reactive with a discontinuous epitope that overlaps the CD4-binding site of gp120. F105 neutralizes laboratory strains of HIV-1 and some primary isolates, and synergizes with other antibodies in neutralizing an expanded spectrum of isolates. Four patients each with CD4 counts between 200 and 500/mm3 received a single dose of F105 at 100 or 500 mg/m2, intravenously. Sustained levels of F105 were obtained in plasma, and there was no evidence of an immune response to F105 as determined by a double-antigen immunoassay. No patient experienced any toxicity. Infused antibody retained full functional activity as detected by the ability of sera to block the binding of labeled F105 to HIV-1-infected cells. Of note, all patients had preexisting antibody to the gp120 CD4-binding site. The ability to culture virus by quantitative microculture remained unchanged by this single dose of antibody. Thus, it can be concluded that F105 is safe and nontoxic as a single injection at the doses tested. Furthermore, the antibody retains full gp120-binding activity. In these patients, with preexisting CD4-binding site antibody, there is no evidence of anti-HIV-1 activity following a single antibody infusion.

L51 ANSWER 9 OF 28 MEDLINE
91031512 Document Number: 91031512. PubMed ID: 2226474. Screening for new agents. Oberg B; Vrang L. (Department of Virology, Karolinska Institute, Stockholm, Sweden.) EUROPEAN JOURNAL OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES, (1990 Jul) 9 (7) 466-71. Ref: 31. Journal code: 8804297. ISSN: 0934-9723. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.
AB Screening for new antiviral drugs is concentrated on a search for inhibitors of the human immunodeficiency virus, herpesviruses, influenza virus, hepatitis B virus and rhinovirus. The first step in the process is usually the screening of virus-infected cell cultures followed by secondary screening in infected animals. The relevance of the different screening methods for predicting clinical efficacy is at present uncertain due to the low number of compounds evaluated in double-blind placebo-controlled clinical trials. As a consequence of the con-siderable activity in ongoing research on antiviral drugs the predictive value of the screening systems is expected to improve.